**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 60 Eighth Street NE<br>Atlanta, GA 30309<br>(404)253-1161 Fax:(404)253-1202<br>ORAPHARM2_RESPONSES@fda.hhs.gov | 11/8/2022-2/10/2023*<br>FEI NUMBER<br>3011158388 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Edward F. Elmore, Chief Quality Officer

| FIRM NAME | STREET ADDRESS |
|---|---|
| Nephron Sterile Compounding Center LLC | 4500 12th Street Ext |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| West Columbia, SC 29172-3025 | Outsourcing Facility |

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

**DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:**
**OBSERVATION 1**
The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

Specifically,

1. Your firm's QCU failed to:

   a. Ensure dynamic smoke studies are conducted: Please refer to **OBSERVATION 2** for details.

   b. Ensure that environmental monitoring limits are validated and not modified: Please refer to **OBSERVATION 2** for details.

   c. Ensure equipment and rooms are maintained for the manufacturing of sterile drug products: Please refer to **OBSERVATION 2**, **OBSERVATION 3,** and **OBSERVATION 13** for details.

   d. Ensure software validations and process validations are performed: Please refer to **OBSERVATION 8** and **OBSERVATION 12** for details.

   e. Quarantine and adequately hold all components, drug product containers, closures, in-process materials, and packaging material stored within your warehouses: Please refer to **OBSERVATION 9** for details.

   f. Implement a proper change control procedure that evaluates manufacturing changes in a manner commensurate with the level of risk imposed by a proposed change: Please refer to **OBSERVATION 11.2** for details.

2. The responsibilities and procedures applicable to the quality control unit are not in writing:

   a. Comprehensive procedures for quality review of audit trails and electronic data review have not been established.

AMENDMENT 1

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b. The electronic data and audit trail review procedures for (b) (4) software used during environmental monitoring (EM) and personnel monitoring (PM) sampling and analysis does not include details of what the reviewers will look for in the various audit trails, establish frequencies for searching for unapproved data, or require documentation of these activities.

c. Procedures do not require all data generated on the systems to be reviewed. For example, but not limited to, the audit trail captured approximately (b) (4) unique sample numbers since April 2022. However, these audit trails are not reviewed to ensure samples have not been manipulated. In addition, your software system has the capability to reprint EM/PM labels at any time. Your software system does not require a justification prior to reprinting. Your firm's IT department identified (b) (4) instances in which EM sample labels were reprinted since installation of this program and (b) (4) instances since FDA's last inspection (04/05/2022).

3. The responsibilities and procedures applicable to the quality control unit are not followed:

a. According to your firm's VP of Quality, your firm uses (b) (4) in all sterile injectable drug products. For example, but not limited to,

i. Since April 2022, your firm missed at least (b) (4) instances in which your (b) (4) was not sampled according to your firm's sampling schedule.

ii. Since 2018, your firm has not tracked and trended (b) (4) sampling in accordance with your firm's established timeframes.

b. Your firm's Quality Assurance (QA) did not follow the review and approval for completed electronic batch records (EBR). For example, but not limited to:

i. Your firm practices (b) (4) the differential pressure within the ISO 5 B/F/S when (non-viable particle) NVP counts are out-of-specification (OOS). However, we observed the timestamps for the (b) (4) differential pressure was documented (b) (4) the timestamp recorded for a NVP count OOS.

c. Your firm's quality personnel do not follow your written procedures that outlines procedures for Microbiology personnel that perform viable surface, viable air, nonviable particulate air, and personnel monitoring sampling. For example, your firm's (b) (4) plates located in the microbiology lab incubator, were missing required information to prevent mix-up.

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4. Your quality unit signed off on batch records that specifically failed to meet the requirements for contact time of your cleaning agents as outlined in your SOP-SC-SR-4530 entitled Area Cleaning and Sanitization for the following:

   a. Norepinephrine Bitartrate Injection 16mcg/mL (Lot (b) (4)) on November 16, 2022; the cleaning of the dispensing corridor and cubby was recorded to clean stainless surfaces and window with (b) (4) and then used (b) (4) for ceiling, floor and walls that start at (b) (4) and ended at (b) (4) ) while (b) (4) requires (b) (4) of contact time followed by (b) (4) and then (b) (4) requires (b) (4) contact time followed by (b) (4) . The cleaning of the formulation suite (b) (4) included cleaning with (b) (4) of the windows, stainless steel surfaces, door handles, trash, chair, EBR Cart, Human Machine Interface (HMI) screen and equipment. (b) (4) was used to clean the floor, ceiling, and walls/doors. The cleaning of the formulation suite was started at (b) (4) and ended at (b) (4) ). The same exact cleaning occurred in formulation suite (M190) starting at (b) (4) and ending at (b) (4) ). These cleaning was performed by one person per the cleaning log. Reviewed and approved by quality on (b) (4) .

   b. Hydromorphone HCl in 0.9% Sodium Chloride Injection 1mg/mL (b) (4) on September 20, 2022, the formulation (b) (4) suite (M109C) was recorded as cleaning the stainless surfaces, window, door handle, push button, trash, and equipment with (b) (4) The floors, ceiling and walls/doors were cleaned with (b) (4) requires (b) (4) of contact time followed by (b) (4) and then (b) (4) requires (b) (4) contact time followed by (b) (4) . The cleaning was recorded as starting at (b) (4) and end time as (b) (4) . The formulation (b) (4) suite (M113) was recorded as cleaning the stainless surfaces, window, door handle, push button, trash and equipment with (b) (4) . The floors, ceiling and walls/doors were cleaned with (b) (4) requires (b) (4) of contact time followed by (b) (4) and then (b) (4) requires (b) (4) contact time followed by (b) (4) . The cleaning was recorded as starting at (b) (4) and end time as (b) (4) ). Reviewed and approved by quality on November 16, 2022. Additionally, on September 21, 2022; the cleaning of the dispensing corridor and cubby was recorded to clean stainless surfaces, equipment and window with (b) (4) and then used (b) (4) for ceiling, floor and walls that start at (b) (4) and ended at (b) (4) while (b) (4) requires (b) (4) of contact time followed by (b) (4) and then (b) (4) requires (b) (4) contact time followed by (b) (4) . The cleaning of the formulation suite (M191) included cleaning with (b) (4) of the windows, stainless steel surfaces, door handles, trash, chair, EBR Cart, HMI screen and equipment. (b) (4) was used to clean the floor, ceiling, and walls/doors. The cleaning of the formulation suite was started at (b) (4) and ended at (b) (4) Reviewed and approved by quality on September 21, 2022.

5. The quality unit is responsible for ensuring that all maintenance and/or calibration is completed prior to the equipment being used for commercial production including 503B products. The quality unit failed to ensure that all B/F/S equipment maintenance was

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being conducted as dedicated in SOP-SC-PR-4347, Version 12.0 dated October 31, 2022.

**OBSERVATION 2**
Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.

Specifically,

1. Your (b) (4) Blow/Fill/Seal (B/F/S) equipment is NOT designed to provide unidirectional/laminar flow of ISO 5 class quality first air to where sterile ingredients and compounding sterile products are directly exposed.

2. Your static smoke studies showed ingress of lower quality air from outside the aseptic filling area into the B/F/S ISO 5 zone. The smoke studies that your firm conducted on 7/27/2019 for line (b) (4) 1/24/2020 for line (b) (4) and 8/7/2020 for line (b) (4) under static conditions failed to ensure that airflows do not distribute particles from personnel, process, or machine to a zone of higher classification. Your firm also failed to conduct smoke studies to evaluate airflow patterns under dynamic conditions in the ISO 5 classified (b) (4) of the B/F/S equipment located on lines (b) (4) (b) (4) prior to use in sterile drug production.

3. On 12/16/2022, an opening/hole, approximately 1/4" in diameter, was observed around the viable particle probe, located on the upper wall inside the ISO 5 (b) (4) of the (b) (4) B/F/S equipment on Line (b) (4) - a design flaw, which increases the potential of contamination from the outside.

4. According to your B/F/S Lead Line Technician, your firm practices the (b) (4) of RPMs on

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your HEPA fan when your (b) (4), a critical parameter, are out-of-specification, (b) (4) the pressure differential within the ISO 5 (b) (4) until (b) (4) are less than or equal to (b) (4). Your B/F/S Lead Line Technician stated this is "(b) (4)." However, this practice is not outlined in any of your firm's written procedures.

Your firm's quality unit did not provide any scientific justification supporting your firm's differential pressure limits in the ISO 5 (b) (4) (see table below) to establish controls preventing the ingress of particles from lesser quality air (ISO 7) into higher quality air (ISO 5). In addition, the acceptable minimum and maximum blower speeds for the HEPA fans or the RPM adjustment values are not documented in your firm's batch records.

| Location on B/F/S | Classification | Pressure Differential Limit |
|---|---|---|
| Line (b) (4) | ISO 5 | (b) (4) |
| Line (b) (4) | ISO 5 | |
| Line (b) (4) | ISO 5 | |

Your firm uses the (b) (4) B/F/S on lines (b) (4) to produce the following sterile 503B drug products:

- Albuterol Sulfate inhalation Solution 05%, 100mg/20mL (5mg/mL) Preservative Free
- Diltiazem HCl Injection in 0.7% NaCl IV Bottle 125mg/125mL
- Epinephrine Injection Vial, USP 1mg/10mL
- Midazolam Injection, USP, IV Bottle 100mg/100mL Preservative Free
- Norepinephrine Bitartrate Injection, USP IV Bottle 16mg/250mL
- Norepinephrine Bitartrate Injection, USP IV Bottle 4mg/250mL

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- Norepinephrine Bitartrate Injection, USP IV Bottle 8mg/250mL
- Phenylephrine HCl in 0.9% Sodium Chloride, USP 50mg/250mL
- Phenylephrine HCl Injection Vial, USP 0.4mg/10mL
- Phenylephrine HCl Injection Vial, USP 0.8mg/10mL
- Phenylephrine HCl Injection Vial, USP 1mg/10mL
- Succinylcholine Chloride Injection Vial, USP 200mg/10mL Preservative Free

**OBSERVATION 3**

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Specifically,

On 02/08/2023, we observed what appears to be rust on the blow-fill-seal (B/F/S) line (b) (4), which is located approximately 41" from the (b) (4) used to cut the (b) (4) during sterile drug production.

Your firm uses the (b) (4) B/F/S on line (b) (4) to produce the following sterile 503B drug products:

- ☐ Albuterol Sulfate inhalation Solution 05%, 100mg/20mL (5mg/mL)-Preservative Free
- ☐ Epinephrine Injection Vial, USP 1mg/10mL
- ☐ Phenylephrine HCl Injection Vial, USP 0.4mg/10mL
- ☐ Phenylephrine HCl Injection Vial, USP 0.8mg/10mL
- ☐ Phenylephrine HCl Injection Vial, USP 1mg/10mL
- ☐ Sodium Chloride Injection, USP
- ☐ Succinylcholine Chloride Injection Vial, USP 20mg/mL Preservative Free (5mL and 10mL)

**OBSERVATION 4**

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Routine calibration of automatic equipment is not performed according to a written program designed to assure proper performance.

Specifically,

1. During our walk-through of the blow-fill-seal (B/F/S) lines on 11/9/2022, we observed a (b) (4) human-machine interface (HMI) screen, which showed the number of run hours until maintenance is due. The (b) (4) screen showed the maintenance due for (b) (4) (b) (4) B/F/S lines (Lines (b) (4) and Line (b) (4). Of the (b) (4) lines, (b) (4) had overdue warning alarms for maintenance. For example, Line (b) (4) (NPC product line) was overdue for Level (b) (4) hours) and Level (b)( maintenance (b) (4) hours) both of which are considered critical maintenance levels. Line (b) (4) (503B product line) was overdue for Level (b)( maintenance (b) (4) hours).

2. On 12/9/2022, during our review of Preventive Maintenance for the (b) (4) Blow/Fill/Seal Machines (Lines (b) (4) your firm was unable to determine whether maintenance was performed as required in SOP-SC-PR-4347, (b) (4) B/F/S Machine Preventive Maintenance. Further, the firm could not determine if the recorded machine hours were from the correct source. For example, your firm recorded the same machine hours of (b) (4) for three (3) months (March, April, and May 2021) for Line (b) (4) (Level (b)( maintenance) despite production occurring on this B/F/S line. Machine hours increase when the B/F/S is in use; therefore, the machine hours would be different.

**OBSERVATION 5**
Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically,

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***THIS IS A REPEAT OBSERVATION***

1. Your firm's Environmental Monitoring technicians, who are trained to conduct sampling, failed to employ proper fingertip swabbing techniques during personnel monitoring of production staff for Hydromorphone 50mg/50mL batch (b) (4) on 9/25/2022, Anticoagulant 200mg/5mL batch (b) (4) on 9/25/2022, Bupivacaine 62.5mg/50mL batch (b) (4) on 10/31/2022, Hydromorphone 6mg/30ml batch (b) (4) on 10/31/2022, and Amino Acid 50mg/mL batch # (b) (4) on 11/8/2022. Technicians were observed (b) (4) fingertips to each media plate, rather than rolling their fingers to capture the gloved hands utilized during aseptic production.

***THIS IS A REPEAT OBSERVATION***

2. According to SOP-SC-MB-4511, Version 32.0 dated October 16, 2022, Section 7.1.4, "For personnel monitoring of gloves, personnel being sampled are (b) (4) (b) (4) ." Your production and QA staff sanitized their gloved hands (b) (4) for personnel monitoring during the following drug production:

| Date | 503B Product | Lot Number | Expiration Date | Distributed |
|---|---|---|---|---|
| 9/25/2022 | Hydromorphone 50mg/50mL | (b) (4) | 3/20/2023 | Yes |
| 9/25/2022 | Anticoagulant 200mg/5mL | | 3/22/2023 | Yes |
| 10/31/2022 | Bupivacaine 62.5mg/50mL | | 4/26/2023 | Yes |
| 10/31/2022 | Hydromorphone | | 4/27/2023 | No |

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| | | | | |
|---|---|---|---|---|
| | 6mg/30ml | | | |
| 11/8/2022 | Amino Acid 50mg/mL | (b) (4) | 2/3/2023 | Yes |

3. Sampling plans do not describe specific locations for collecting surface samples to ensure reproducible results and that the highest risk locations are sampled. For example, but not limited to, your firm's written procedures for environmental and personnel monitoring includes a sample checklist for your firm's (b) (4) B/F/S Line (b) (4). However, your firm's environmental monitoring sampling plan does not include any surface sampling inside the (b) (4) or (b) (4) (b) (4) (critical fill area), which come in direct contact with sterile drug product.

4. Your firm failed to conduct an assessment to show the probes for the viable and non-viable particles are placed in the most critical locations inside the ISO 5 classified (b) (4) of the (b) (4) Blow/Fill/Seal (B/F/S) equipment. Active air environmental sampling within the (b) (4) is not representative of the filling process.

5. Your firm failed to place the (b) (4) probe within the ISO 5 Laminar Flow Hood (LFH), located in (b) (4) and (b) (4), where (b) (4) aseptic operations take place and in an orientation that provides meaningful data. For example, but not limited to, the (b) (4) probe is placed (b) (4) of where aseptic operations occur and is not positioned pointing into the airflow.

**OBSERVATION 6**
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include adequate validation of the aseptic process.

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1. During our observation of aseptic processing of Hydromorphone 10mg/50mL batch (b) (4) on 11/8/2022, we observed the following:

   a. Both production and QA personnel grasping the syringe plunger during aseptic processing in both ISO 5 and ISO 7 classified areas.

   b. The Filler and Capper having a conversation while working inside the ISO 5 classified aseptic processing area.

   c. The Filler and Capper moving their heads in and out of the ISO 5 classified aseptic processing area.

   d. The Sterile Filling Supervisor picking up a computer cord that fell on the floor in the ISO 7 classified area.

2. According to your video footage (b) (4) during aseptic processing of 503B drug products in classified rooms, M122 and M123, we observed multiple personnel engaged in improper practices:

   a. On 9/25/2022 during aseptic processing of Hydromorphone 50mg/50mL batch # (b) (4) EXP: 3/20/2023, we observed the following:

      i. Items introduced into ISO 5 hood without sanitizing

      ii. Rapid movements inside ISO 5 hood

      iii. Grasping syringe plunger in both ISO 5 and ISO 7 classified areas

      iv. Not performing aseptic processing 6" inside ISO 5 hood

      v. Arms resting on the surface of ISO 5 classified aseptic processing area

      vi. Not exposing critical site of sterile product to first pass air during hand off in ISO 5 hood

      vii. Talking while performing aseptic manipulations inside ISO 5 hood

      viii. Trash bag on cart holding finished drug products in ISO 7 area

   b. On 9/25/2022 during aseptic processing of Anticoagulant 200mg/5mL batch (b) (4) EXP 3/22/2023, we observed the following:

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|---|---|
| Edward F. Elmore, Chief Quality Officer | |
| FIRM NAME<br>Nephron Sterile Compounding Center LLC | STREET ADDRESS<br>4500 12th Street Ext |
| CITY, STATE, ZIP CODE, COUNTRY<br>West Columbia, SC 29172-3025 | TYPE ESTABLISHMENT INSPECTED<br>Outsourcing Facility |

i. Items introduced into ISO 5 hood without sanitizing
ii. Grasping syringe plunger in both ISO 5 and ISO 7 classified areas
iii. Arms resting on the surface of ISO 5 classified aseptic processing area
iv. Not exposing critical site of sterile product to first pass air during hand off in ISO 5 hood
v. Talking while performing aseptic manipulations inside ISO 5 hood
vi. Sterile wipes closure left open in ISO 7 area
vii. Product dropped on surface of ISO 5 classified aseptic processing area but not wasted on batch record

c. On 10/31/2022, during aseptic processing of Bupivacaine 62.5mg/50mL batch # (b) (4) EXP: 4/26/2023, we observed the following:
   i. Grasping syringe plunger in both ISO 5 and ISO 7 classified areas
   ii. Not performing aseptic processing 6" inside ISO 5 hood
   iii. Arms resting on the surface of ISO 5 classified aseptic processing area
   iv. Not exposing critical site of sterile product to first pass air during hand off in ISO 5 hood
   v. Talking while performing aseptic manipulations inside ISO 5 hood
   vi. Sterile wipes closure left open in ISO 7area
   vii. Trash bag on cart holding finished drug products in ISO 7 area

d. On 10/31/2022, during aseptic processing of Hydromorphone 6mg/30ml batch (b) (4) EXP: 4/27/2023, we observed the following:
   i. Grasping syringe plunger in both ISO 5 and ISO 7 classified areas
   ii. Touching outer part of glove then not sanitizing
   iii. Arms resting on the surface of ISO 5 classified aseptic processing area
   iv. Not exposing critical site of sterile product to first pass air during hand off in ISO 5 hood

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v. Talking while performing aseptic manipulations inside ISO 5 hood

e. On 11/8/2022, during aseptic processing of Amino Acid 50mg/mL batch (b) (4) EXP: 2/3/2023, we observed the following:

i. Touching goggles on face without sanitizing afterwards

ii. Sterile wipes closure left open in ISO 7 area

iii. Trash bag on cart holding finished drug products in ISO 7 area

3. Your firm performed a total of (b) (4) 503B media fills from April to December 2022, of which (b) (4) of the fills had filled units held in a segregated portion (media fill suite) of the API warehouse that was not temperature mapped for prolonged periods. Your firm's procedure SOP. CM. 1604, Aseptic Process Simulation - Media Fill is silent to the duration filled media units can be held before incubation. You held filled media units for periods of (b) (4) before incubation began. Your firm's failure to immediately incubate the filled media units at the optimal incubation temperature and time, could potentially result in media that is not suitable for recovery of bioburden and environmental isolates.

4. Your firm's B/F/S in lines (b) (4) have not been validated to assure that all bioburden of non-sterile resin to show that the B/F/S process can adequately reduce the bioburden adequately to assure sterility assurance of all sterile products produced on these lines. Additionally, the (b) (4) room that resin is stored in is not properly temperature regulated and not monitored for humidity.

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**OBSERVATION 7**

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

Specifically,

Document# MP-015-SR, Cleaning, Sanitizing, and Disinfecting Agent Efficacy Study at The Nephron

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Pharmaceuticals South Carolina Facility, effective 7/10/17, has not demonstrated that the current disinfectants used in the sterile drug product manufacturing area are effective in preventing or reducing microbial contamination. MP-015-SR, approved 7/10/17, was found to be inadequate for the following reasons:

1. Your firm's disinfectant efficacy study is missing test organism (b) (4) data used to determine the colony-forming units (cfu) counts used in the study. Specifically, the (b) (4) scheme data was not recorded in Laboratory notebook NL-17-039, (used to document MP-015-SR study data) for six of the seven bacteria, and for the one yeast and one mold used in MP-015-15.

2. You have not considered surfaces in the aseptic filling area. Specifically, not all critical surface areas/materials used to manufacture or introduce drug components into "critical" areas were included in the MP-015-SR, specifically (b) (4) (material: (b) (4) , which is used to introduce drug components into a filling area for B/F/S line (b) (4) room (b) (4) was not included in the study.

3. Additionally, as outlined in the section "2.0 General Acceptance Criteria"- "a sanitizing/disinfectant agent will be considered effective when used on a surface material type if not less than a (b) (4) reduction from the initial microbial concentration is observed, and/or not less than a (b) (4) reduction is observed in spore forming microorganisms., (b) (4) of incubation for microbial vegetative bodies." Incubation times of (b) (4) were not met for 5 bacteria and 1 mold disinfectant combination(s).

**OBSERVATION 8**

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Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Specifically,

1. The Programmable Logic Controls (PLC) for the Blow/Fill/Seal (B/F/S) for Line (b) (4) uses a shared username and password and does not have audit trails. Controls have not been established to ensure there are no changes made to critical operating parameters. Your firm's PLC allows any user with access to make unrestricted manipulations during the production of sterile injectable drug products. For example, your firm (b) (4) the RPMs in the air handling unit within the ISO 5(b) (4) (critical zone) to (b) (4) the dynamic airflow to reach particle counts within acceptable limits.

   In addition, your firm's written procedure establishes HEPA(b) (4) testing/recertification should include integrity testing of the HEPA filters, particle counts, and air velocity checks to ensure that appropriate air flow and quality is maintained. However, your firm's HEPA filter integrity tests do not include an evaluation with the(b) (4) RPMs ensuring appropriate air flow and quality is maintained within this critical zone.

   Furthermore, Investigation, SC.ER.MB.22.117, states the B/F/S technician (b) (4) ISO 5 (b) (4) (critical zone). (b) (4) ".

2. Your firm failed to demonstrate the reliability of automated systems. For example, but not limited to, your firm uses a PLC on your HMI that has not been validated for use for your B/F/S lines.

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**OBSERVATION 9**
The control systems necessary to prevent contamination or mix-ups are deficient.

Specifically,

Your firm failed to ensure that all production components are received in a manner that allows for full inventory control and reconciliation as the items are further dispositioned. For example, but not limited to:

1. Your firm's (b) (4) failed to properly reconcile 503B drug components. In addition, your firm stored these components, both expired and within expiry, in locations not designed to adequately store 503B drug component.

   a. On 11/10/2022, we observed (b) (4) consisting of (b) (4) different drug components stored in your firm's vaccine wing, which has been under construction since October 2020, without qualified temperature/humidity controls. According to your Assistant Component Assembly Manager, your firm has stored these expired and overstocked 503B drug components in this non-designated area since February 2022. Your firm's Warehouse Inventory Manager was unable to successfully locate these 503B drug components within (b) (4)

   b. On 11/15/2022, we observed 503B drug components at your off-site Calhoun Warehouse, which is not temperature and humidity controlled or serviced for pest control. These drug components were used in the production of sterile 503B finished products, for example, but not limited to:

| Lot Number | 503B Product | Quantity |
|---|---|---|

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| | | |
|---|---|---|
| (b) (4) | 8.4% Sodium Bicarbonate Inj, USP 4.2g/50mL | (b) (4) syringes |
| (b) (4) | 8.4% Sodium Bicarbonate Inj, USP 4.2g/50mL | (b) (4) syringes |
| (b) (4) | 8.4% Sodium Bicarbonate Inj, USP 4.2g/50mL | (b) (4) syringes |

2. There is a systemic failure of your firm's inventory management process to maintain accurate count and location of current on-hand inventory of 503B components.

   a. For example, but not limited to, on 11/10/2022 and 11/11/2022, we found the following inventory discrepancies on three randomly selected 503B components stored in your firm's vaccine wing:

| Component Description | Component Lot Number | Quantity Shown in (b) (4) | Actual Quantity On-Hand | Quantity Discrepancy |
|---|---|---|---|---|
| (b) (4) | | | | |

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b. Your Warehouse Inventory Manager pulled up an Inventory Worksheet for all components currently designated to the Calhoun Warehouse location in (b) (4) A query on (b) (4) for the Production Components Inventory Worksheet on (b) (4) syringes lot (b) (4) and (b) (4) bags lot (b) (4) that were listed on the Calhoun Warehouse Inventory Worksheet showed they were located at the main Nephron facility. The two reports both generated on (b) (4) showed different locations for the same lot components.

3. On November 8, 2022, during our walkthrough of your raw materials warehouse, it was confirmed by your Raw Material Logistic Manager and Quality Assurance Inspection Manager that your raw materials are not segregated in a separate location for quarantine, release or hold items. The raw materials are not marked quarantined to visually indicate that the raw material is quarantined. Instead, the firm relies solely on their inventory management system.

4. Your firm stores products and components in your warehouse that are unaccounted for by (b) (4)

   a. On November 8, 2022, during our walkthrough of your raw materials warehouse, it was noted that raw materials on the bottom shelf of (b) (4) were not maintained in your inventory management system. Your Raw Material Logistic Manager and Quality Assurance Inspection Manager for Raw Materials confirmed that these products are stored in this location until needed then added into your inventory management system at that time.
   b. On November 9, 2022, during our walkthrough of your Distribution Center (DC) warehouse, we observed pallets with signage affixed stating "Do Not Waste" per your Chief Executive Officer. We asked your Warehouse Inventory Manager to determine the status for the following items contained on the pallets:
      i. (b) (4) Syringe Barrel (20mL) lot (b) (4)

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ii. (b) (4) Plunger Rod (20mL) lot (b) (4)
iii. (b) (4) Syringes (20mL) lot (b) (4)

Your Warehouse Inventory Manager and Vice President of New Products confirmed that the material was not in (b) (4) the firm's inventory management system. Further, your warehouse leadership could not readily provide details explaining how the materials circumvented your inventory management system and arrived in the warehouse.

**OBSERVATION 10**
Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

Specifically,

1. Raw data recorded in the study binder, used to document study data for Validation of a (b) (4) (b) (4) (MP-129-SR), is missing (b) (4) data used to determine the colony-forming units (cfu) counts for the microorganisms used in the study.

2. The in-house fungal isolates and the purchased microorganisms used in MP-129-SR, Validation of a (b) (4) study, are not listed in the materials used in this study.

3. While the incubation temperatures were listed in MP-129-SR, as (b) (4) and (b) (4) the actual incubators used were not identified as either (b) (4) making it impossible to verify the test organisms were incubated at the appropriate temperature.

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**OBSERVATION 11**
Written production and process control procedures are not followed in the execution of production and process control functions.

Specifically,

1. Your firm's quality personnel do not follow your firm's written procedure that governs documentation practices are contemporaneous and do not follow your firm's written procedure that describes labeling of (b) (4) sampling plates used during environmental and personnel monitoring.

   For example, your firm's EM Assistant Manager, EM Program Manager, Director of Microbiology, and QC Microbiology Manager explained printed labels are placed on (b) (4) plates after sampling is completed to ensure times printed on the printed label captures the time at which sampling was performed. In addition, when a printer is not immediately available and to ensure the correct labels are placed on corresponding (b) (4) sampling plates, a cleanroom marker is used to capture the following information on the surface of the (b) (4) plate: Sample location, Date/time, Sampling Technician, Media lot number used, and the Applicable Batch/Lot information. However, we observed multiple labels that were printed with the same timestamp on your firm's (b) (4) sampling plates. For example, but not limited to:

| Sample ID | Location | Date/Time |
|---|---|---|
| (b) (4) | | |

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(b) (4)

2. Your firm failed to acknowledge/follow your established change control procedure. For example, you installed and modified (b) (4) B/F/S machines (Serial Numbers: (b) (4) (b) (4) on lines (b) (4), respectively. According to your firm's Executive Vice President of Manufacturing, the firm added "(b) (4) to decrease particle count within the ISO 5 and ISO 7 environment utilizing a (b) (4)." You did all of this without utilizing your established change management system to address this change. Furthermore, the qualification of the B/F/S machines did not account for these

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modifications, and only included evaluation of the Original Equipment Manufacturing (OEM) specifications. Finally, your firm was unable to provide design specifications, updated drawings of the modifications, or provide original verification of the material of construction (MOC).

**OBSERVATION 12**
Control procedures are not established which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically,

Since 2020, your firm has manufactured (b) (4) lots of Albuterol Sulfate inhalation Solution 05%, 100mg/20mL (5mg/mL)-Preservative Free on (b) (4) BFS Line(b) (4) (503B), of which, (b) (4) lots (b) (4) were distributed between 2020-2021. According to your firm's Vice President of Validation, your firm failed to perform a process validation for this drug product.

**OBSERVATION 13**
Buildings used in the manufacturing and processing of a drug product are not maintained in a good state of repair.

Specifically,

1. On 12/12/2022 during our walk through of the (b) (4) B/F/S lines, we observed at least (4) four openings approximately 1" in diameter surrounding the pipes in the ceiling of room 172B that exposes the ISO 7 room to the lesser quality air from the non-classified plenum space above.

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Line (b) (4) which has been in production since 2019, is in room 172B and has been used to produce (b) (4) lots of sterile 503B drug products, of which (b) (4) units are within expiry.

2. On 02/08/2023, we observed at least (3) openings, approximately 1" in diameter surrounding the pipes in the ceiling of room 174B that exposes the ISO 7 room to the lesser quality air from the non-classified plenum space above. Line (b) (4) which has been in production since 2020, is in room 174B and has been used to produce (b) (4) units of sterile 503B drug products since January 2022, that are within expiry.

3. On 12/14/2022, while evaluating the modifications made on the (b) (4) B/F/S machine on line (b) (4) located in room 172B (ISO 7), we observed duct tape used to hold together the "particulate matter (b) (4) " located approximately 3" from the (b) (4) used to cut the (b) (4) during sterile drug production.

**OBSERVATION 14**
Employees are not given training in the particular operations they perform as part of their function.

Specifically,

1. Your QA Visual Inspection staff, who were trained on 503B (b) (4) Examination Process per the new SOP.QA.3212 on 12/30/2022, failed to correctly document their examination and to use the correct form for documentation. Furthermore, your QA staff signed off on the second verification and the final QA review without identifying these errors.

2. Your QA Incoming Inspectors, who currently conduct (b) (4) inspection of the raw materials

AMENDMENT 1

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|---|---|---|---|
| | Sonya M Edmonds, Investigator<br>Song Y Lavalais, Investigator<br>June P Page, Investigator<br>Mary-Jeanet Mcgarry, FDA Center Employee<br>Jamie L Port, Microbiologist<br>Melanie M Walker, Microbiologist<br>Clifton L Randell, Microbiologist | X Sonya M Edmonds Investigator Signed By: Sonya M. Edmonds -S Date Signed: 02-10-2023 13:20:02 | 2/10/2023 |

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 60 Eighth Street NE<br>Atlanta, GA 30309<br>(404)253-1161 Fax:(404)253-1202<br>ORAPHARM2_RESPONSES@fda.hhs.gov | 11/8/2022-2/10/2023*<br>FEI NUMBER<br>3011158388 |

| NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED | |
|---|---|
| Edward F. Elmore, Chief Quality Officer | |
| FIRM NAME<br>Nephron Sterile Compounding Center LLC | STREET ADDRESS<br>4500 12th Street Ext |
| CITY, STATE, ZIP CODE, COUNTRY<br>West Columbia, SC 29172-3025 | TYPE ESTABLISHMENT INSPECTED<br>Outsourcing Facility |

reserve samples, have not been trained on one or both of the following required training codes: SOP.QA.3207 Retain Samples - Sampling and Storage and SOP-SC-QA-3250 Retain Samples - Sampling and Storage. As a result, they failed to record the disposal date on the actual reserve sample label once a raw material folder was closed and dispose of the reserve samples according to the firm's specified retention time. For example, but not limited to, the following discrepancies were discovered during our review of the controlled substance raw material reserve samples:

a. On 12/9/2022, your firm had the following controlled substance reserve samples with missing disposal dates written on the label despite their raw material folder being closed in (b) (4)
   i. RM container # (b) (4)
   ii. RM container #
   iii. RM container #
   iv. RM container #
   v. RM container #

b. On 1/31/2023, your firm had the following controlled substance reserve samples with missing disposal dates written on the label despite their raw material folder being closed in (b) (4)
   i. RM container # (b) (4)
   ii. RM container #
   iii. RM container #

c. On 12/9/2022, your firm had the following controlled substance reserve samples still in your inventory despite them being beyond their disposal date:
   i. RM container # (b) (4)

AMENDMENT 1

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| NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED | |
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| Edward F. Elmore, Chief Quality Officer | |
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| CITY, STATE, ZIP CODE, COUNTRY<br>West Columbia, SC 29172-3025 | TYPE ESTABLISHMENT INSPECTED<br>Outsourcing Facility |

ii. RM container #(b) (4)
iii. RM container #(b) (4)
iv. RM container #(b) (4)
v. RM container #(b) (4)
vi. RM container #(b) (4)
vii. RM container (b) (4)
viii. RM container #(b) (4)
ix. RM container #(b) (4)

d. On 1/31/2023, your firm had the following controlled substance reserve samples still in your inventory despite them being beyond their disposal date:
   i. RM container #
   ii. RM container (b) (4)

**OBSERVATION 15**
Reserve samples of active drug ingredients are deficient in that they are not retained at least one year after the expiration date of the last lot of the drug containing the active drug ingredient.

Specifically,

Your firm failed to retain reserve samples for (b) (4) the expiration date of the last lot of drug product containing that reserve sample as stated in your firm's procedures, SOP.QA.3207. The following reserve samples were wasted prior to the required retention date: Neostigmine Methylsulfate (b) (4) and Norepinephrine Bitartrate (b) (4)

***DATES OF INSPECTION**

AMENDMENT 1

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| | Sonya M Edmonds, Investigator<br>Song Y Lavalais, Investigator<br>June P Page, Investigator<br>Mary-Jeanet Mcgarry, FDA Center Employee<br>Jamie L Port, Microbiologist<br>Melanie M Walker, Microbiologist<br>Clifton L Randell, Microbiologist | X Sonya M Edmonds Investigator Signed By: Sonya M. Edmonds -S Date Signed: 03-10-2023 13:20:02 | 2/10/2023 |

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
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| 60 Eighth Street NE<br>Atlanta, GA 30309<br>(404)253-1161 Fax:(404)253-1202<br>ORAPHARM2_RESPONSES@fda.hhs.gov | 11/8/2022-2/10/2023*<br>FEI NUMBER<br>3011158388 |

| NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED | |
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| Edward F. Elmore, Chief Quality Officer | |
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| CITY, STATE, ZIP CODE, COUNTRY<br>West Columbia, SC 29172-3025 | TYPE ESTABLISHMENT INSPECTED<br>Outsourcing Facility |

11/08/2022(Tue), 11/09/2022(Wed), 11/10/2022(Thu), 11/11/2022(Fri), 11/14/2022(Mon), 11/15/2022(Tue), 11/16/2022(Wed), 12/07/2022(Wed), 12/08/2022(Thu), 12/09/2022(Fri), 12/12/2022(Mon), 12/13/2022(Tue), 12/14/2022(Wed), 12/15/2022(Thu), 12/16/2022(Fri), 1/30/2023(Mon), 1/31/2023(Tue), 2/01/2023(Wed), 2/02/2023(Thu), 2/03/2023(Fri), 2/06/2023(Mon), 2/07/2023(Tue), 2/08/2023(Wed), 2/09/2023(Thu), 2/10/2023(Fri)

X June P Page
Investigator
Signed By: 2000405709
Date Signed: 02-10-2023 13:22:10

**AMENDMENT 1**

| | EMPLOYEE(S) SIGNATURE | | DATE ISSUED |
|---|---|---|---|
| **SEE REVERSE OF THIS PAGE** | Sonya M Edmonds, Investigator<br>Song Y Lavalais, Investigator<br>June P Page, Investigator<br>Mary-Jeanet Mcgarry, FDA Center Employee<br>Jamie L Port, Microbiologist<br>Melanie M Walker, Microbiologist<br>Clifton L Randell, Microbiologist | X Sonya M Edmonds<br>Investigator<br>Signed By: Sonya M. Edmonds -S<br>Date Signed: 02-10-2023<br>13:20:02 | 2/10/2023 |

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."